

Appl. No. : 10/698,343
Filed : October 31, 2003

SUMMARY OF INTERVIEW

Applicants wish to thank Examiner Fernandez for the telephone interview with Applicants' representative, Marc Morley, on September 8, 2005.

Exhibits and/or Demonstrations

None.

Identification of Claims Discussed

1-34.

Identification of Prior Art Discussed

Prior art of record was discussed.

Proposed Amendments

None.

Principal Arguments and Other Matters

Examiner Fernandez and Marc Morley discussed the rejections set forth in the Office Action.

Results of Interview

No agreement was reached.

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REMARKS

Upon entry of the above amendments, Claims 1-18, 21-34 and 45-56 are presented for examination. Claims 19-20 and 35-44 have been cancelled without prejudice. New Claims 45-56 have been added. Claims 1, 4-5, 9, 15, 17, 21-24 and 30-32 have been amended as set forth above. The additions to the claims are shown by underlined text and the deletions by strike through text.

The new and amended claims are supported by the original claims specification as filed. Therefore, no new matter is added by the addition of new Claims 45-56 or by the amendments to Claims 1, 4-5, 9, 15, 17, 21-24 and 30-32.

Discussion of Claim Objection

The Examiner objected to Claim 15, 17 and 19 for use of the phrase "further wherein." The term "further" has been deleted from the objected to claims, therefore, the objection is moot.

Discussion of Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 1-34 under 35 U.S.C. § 112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards the invention.

The Examiner rejected Claim 1 as indefinite for use of the terms "substantially" and "effective." In particular, the Examiner argues that it is not clear what constitutes a "substantially stationary position." Also, the Examiner argues that it is not clear what makes the "distance" effective or how the "distance" is effective.

Furthermore, the Examiner asserts that it is unclear how one would practice claimed method without knowing the location of one or more cells. The Examiner states that "[t]o a certain degree, the position of any vessel containing cells should be known to ensure that there even exists a probability that one or more cells is/are coincident with the path of electromagnetic radiation." Finally, the Examiner states that it is not clear who should be without prior knowledge of the location.

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Claim 1 has been amended as set forth above to delete the allegedly indefinite phrases "substantially stationary position" and "effective distance." Also, as stated above, the Examiner asserts that Claim is confusing because of the phrase "without prior knowledge of the specific three-dimensional location of said one or more cells." Respectfully, the phrase is clear and definite. Nonetheless, as a clarification paragraph [0073] in relevant part states that "[t]he methods ... described herein do not require knowledge of the specific three-dimensional locations of cells in order to induce a transient state of permeability ... [i]nstead, the cells to be transiently permeabilized can exist within a defined volume, wherein the defined volume has known dimensions and position in space." The position of the vessel or container of the cell(s) is known, however, the specific three-dimensional position of any given cell may not be known prior to directing the electromagnetic to a location within the cell containment device. As one example, paragraph [0121] states "[a]n area of the well was exposed to a predetermined grid pattern of laser shots that did not require locating the target cells prior to shooting." This means that the electromagnetic radiation was directed to a location of the cell containment device without knowing if a cell was at the particular location. Respectfully, the phrase "without prior knowledge" is clear and definite in view of the specification.

In view of the above discussion, Applicants submit that Claim 1 is clear and definite.

Applicants note the addition of new Claims 45-56. New Claims 47 and 56 use the phrase "substantially stationary position" and that new Claims 45, 48 and 56 use the phrase "within an effective distance." Respectfully, the phrases are not indefinite as they are defined in the specification in paragraph [0073], which in relevant part recites:

The cells preferably can be in a substantially stationary position within the defined volume, wherein substantially stationary means that the cells are not crossing the boundaries of the defined volume (either into or out from the defined volume) during the irradiation process. The defined volume is partly bounded by a defined area on a solid surface, wherein the defined area has known dimensions and position on the solid surface. The defined area can have a variety of useful sizes and/or boundaries (e.g., the area on the inside bottom surface of a single well of a multi-well tissue culture plate, or the area on the inside bottom surface of a tissue culture flask), depending upon the application of the invention, including but not limited to: at least 0.0001, 0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 200, 300 and 400 square centimeters. The defined volume further can be bounded by an effective distance projected orthogonally away from the defined area, wherein the effective

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distance is a predetermined distance within which the electromagnetic radiation is known to be effective for the purpose of inducing a transient state of permeability in a cell (Figure 1).

Also, the description of Figure 1 in paragraph [0060] recites:

Figure 1 is a perspective view of a defined volume (V, measuring x by y by d), depicting a defined area (A, measuring x by y) on a solid surface (S) and an effective distance (d) projected orthogonally away from the defined area. Also shown are several cells existing within the defined volume, and a substantially transparent solid material (M) forming the solid surface.

Respectfully, the rejected phrases are clear and definite as they are defined in the specification. The phrase "substantially stationary" is defined in the specification: "substantially stationary means that the cells are not crossing the boundaries of the defined volume (either into or out from the defined volume) during the irradiation process." The "defined volume" also is described as illustrated by the above citations from the specification. Examples of a defined area are provided in paragraph [0073] and elsewhere in the specification. The phrase "effective distance" is clearly described in the specification as "a predetermined distance within which the electromagnetic radiation is known to be effective for the purpose of inducing a transient state of permeability in a cell."

Respectfully, Applicants submit that the phrases "substantially stationary position" and "within an effective distance" are clear and definite as used in the claims.

The Examiner rejected Claims 8, 9, 23, 24 and 26 as indefinite for use of the phrase "wherein said directing comprises ..." According to the Examiner, "[i]t is not clear how the process of 'directing' radiation can comprise of delivering a pulse or pulses of radiation or passing a beam of radiation across a surface.

Respectfully, the specification clearly describes the above-rejected phrases. For example, paragraph [0077] discusses directing pulses of radiation to a location. That paragraph also describes passing a beam, stating that the radiation beam can be continuous and that the continuous beam can be passed across the defined area. Thus, the radiation can be directed to a location in the form of a pulse or passed across an area in a continuous beam. In view of the above, Applicants assert that the phrases are clear and definite.

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The Examiner rejected Claims 16 and 18 arguing that the phrase "modified nucleic acid" is indefinite. According to the Examiner, it is not clear what modifications are appropriate for a nucleic acid to be considered "modified."

The claimed methods can be used to permit the entry or withdrawal of a variety of substances into or out of a cell. Modified nucleic acids are examples of such substances. Those of ordinary skill in the art are familiar with numerous "modified nucleic acids." One example of a modified nucleic acid is a peptide nucleic acid (*see* paragraph [0088]). Modified nucleic acids are well known to those of ordinary skill in the art, and as such, Claims 16 and 18 are clear and definite.

Also, the Examiner rejected Claims 19 and 20 as indefinite for use of the phrase "substantially non-permeabilized state." Specifically, the Examiner states that it is unclear to what extent the membrane is in a "non-permeabilized state" as required by the term "substantially."

As set forth above, Claim 19-20 have been cancelled without prejudice. Therefore, the indefiniteness rejection of those claims is moot and not discussed further in this response.

The Examiner further rejected Claims 26 and 29 arguing that "[i]t is not clear what 'pulse target pattern' defines." Respectfully, the phrase "pulse target pattern" is clear and definite. Examples of pulse target patterns are described in Examples 1-3. For example, paragraph [0121] states that "pulses were fired and steered sequentially such that the distance between adjacent shots within the predetermined grid pattern was 20 μm in both x- and y-directions." Also, paragraph [0122] states that "[c]ells were optoinjected using shots of 532 nm light in a 25 μm diameter beam, in a grid pattern with 25 micrometer spacing." Finally, as another example, paragraph [0123] states that "pulses were fired and steered sequentially such that the distance between adjacent shots within the predetermined grid pattern was about 50 μm in both x- and y-directions." In view of the above, Applicants assert that Claims 26 and 29 are clear and definite.

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Finally, the Examiner rejected Claim 32 as indefinite because of the phrase "substantially the entirety of said defined area." Also, the Examiner states that the claim recites "said defined are" without antecedent basis.

Claim 32 has been amended as shown above to correct the antecedent basis of the claim. Furthermore, the claim has been amended to delete the word "substantially." Therefore, Claim 32 is clear and definite.

In view of the above discussion, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejections under § 112, second paragraph.

Discussion of Rejections Under 35 U.S.C. § 102

Claims 1, 6-9, 14, 17-20, 23, 25-29 and 32 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kasuya et al. ("Kasuya") (U.S. Patent No. 5,013,660). The Examiner argues that Kasuya teaches the claimed methods. Applicants respectfully disagree.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). Here, Kasuya does not teach each and every feature of pending independent Claims 1, 48 and 56.

The Examiner argues, relying upon column 5, lines 32-37, that Kasuya teaches a method where there is no prior knowledge of the location of a cell. Applicants respectfully submit that Kasuya discloses methods of implanting living cells with a foreign substance where cells are targeted after knowledge of a cell's location is determined. For example, the section referenced by the Examiner describes a cell punching apparatus where the cells are illuminated and their image projected to a TV monitor. *See Kasuya*, column 5, lines 37. The same column at lines 49-55 states that "the stage 14 is driven until the image of a congregation of cells appears in the field of the monitor 18 ... [t]hen the shutter 5 is kept open, thereby permitting the continuous irradiation of the sample holder 15 by the punching laser beam 2." Thus, the cells are punched only after knowledge of their presence and location is determined. Therefore, the embodiment of Kasuya referenced by the Examiner does not disclose all of the features of any of the instant independent claims.

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Furthermore, Applicants note that the other examples disclosed in Kasuya also target a cell with a laser only after receiving knowledge of the location of a cell. For example, column 6, lines 37-42, states that "[t]he detector 25 detects a cell passing by the detector to generate and send a detection signal to a central processing unit 26, and then the central processing unit 26 times the start of the punching laser source 21, thus causing the punching beam to hit the descending cell to make a hole therein." See also Figure 6 of Kasuya. Likewise the apparatus of Figure 7 of Kasuya first detects, then punches with the appropriate laser beam. Furthermore, the apparatus depicted in Figure 8 of Kasuya uses a light pen, a TV monitor, and a spot position determining means in order to locate a cell and then direct the punching beam to the cell. See column 7, lines 28-68. Figure 9 of Kasuya depicts an apparatus where the position of a cell or location on a cell is first determined prior to directing the punching laser to the cell. See column 8, lines 1-42. Finally, column 8, lines 43-49 state that "[t]he embodiments described above use two different laser sources, that is, a punching laser source and reference laser source." Thus, each of the above-discussed examples from Kasuya directs a laser beam to a cell only after determining the presence/location of the cell.

Therefore, Kasuya does not anticipate the independent claims because, for among other reasons, Kasuya does not disclose, in relevant part, a directing step without prior knowledge of the location of said one or more cells or a directing step without prior knowledge of the specific three-dimensional location of said one or more cells. Therefore, reconsideration and withdrawal of the instant rejection under § 102 is respectfully requested.

Discussion of Rejections Under 35 U.S.C. § 103

Claims 1-3, 6-14, 17-20, 23 and 25-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kasuya (discussed above) in view of Koller et al. ("Koller") (U.S. Patent Publication No. 2002/0076744). Claims 1-3, 6-14 and 17-34 are rejected over Kasuya in view of Koller and further in view of Marchitto et al. ("Marchitto") (U.S. Patent No. 6,315,772). Also, Claims 1-14 and 17-34 are rejected over Kasuya in view of Koller, in view of Marchitto, and further in view of Souhayer et al. ("Souhayer") (Anal. Chem., 72:1342-1347 (2000)). Finally, Claims 1-34 are rejected over Kasuya in view of Koller, in view of Marchitto, in view of Souhayer, and further in view of Flock et al. ("Flock") (U.S. Patent No. 6,424,863).

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To establish a *prima facie* case of obviousness all of the claim limitations must be taught or suggested by the prior art. See *In re Royka*, 490 F.2d 981 (CCPA 1974) and M.P.E.P. § 2143.03.

Applicants submit that Claim 1 and new independent Claims 48 and 56 are not obvious over the cited references alone or when combined, because the references do not teach or suggest each and every claim limitation. The deficiencies of Kasuya et al. as applied to Claims 1, 48 and 56 are discussed above. Specifically, Kasuya does not disclose a method where there is no prior knowledge of the location of a cell. The secondary cited references under § 103 (Koller, Marchitto, Souhayer, and Flock) do not disclose the missing features of those claims and lack additional features.

Koller discloses optoinjection methods. Generally, Koller discloses methods that include the step of "locating a target cell." Marchitto discloses a method of removing fluids, gases or other biomolecules, or delivering a pharmaceutical composition, through the skin of a patient without the use of a sharp or needle. The method of Marchitto includes the step of irradiating the stratum corneum, an applied pharmaceutical or an absorbing material, using a laser. Souhayer discloses the technique of optoporation, which is very different from the optoinjection technique of Kasuya. Souhayer focuses the energy source not to coincide with cells, but to coincide with the coverslip/buffer interface, and the resulting shock wave causes permeabilization of the membranes of nearby cells. Finally, Flock discloses methods that target tissue with electromagnetic energy in order to permit passage of substances into or out of the tissue.

Thus, none of the references overcome the above-described deficiencies of Kasuya. Further, none of the references alone or in combination disclose all of the limitations of any claim. Therefore, amended Claim 1 and new independent Claims 48 and 56 cannot be obvious over the cited references. Applicants respectfully request reconsideration and withdrawal of the instant obviousness rejection.

Conclusion

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is in condition for allowance. Accordingly, Applicant requests the expeditious allowance of the pending claims.

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The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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